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Albumin homeostasis in patients undergoing continuous ambulatory peritoneal dialysis

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Albumin homeostasis in patients undergoing continuous ambulatory peritoneal dialysis. Albumin and protein removal rates were studied in 18 patients undergoing continuous ambulatory peritoneal dialysis (CAPD). In nine patients simultaneous studies of albumin distribution and turnover were performed. Total albumin loss was 4.23 ± 1.42 g/1.73 m^2/24 hr; total protein removed was 8.79 ± 4.21 g/1.73 m^2/24 hr. Although these values were well within the range for severe nephrosis, serum albumin concentration remained nearly normal, 3.7 ± 0.5 g/dl. Plasma albumin mass, 120.0 ± 25.2 g/1.73 m^2, and total albumin mass, 249 ± 29.1 g/1.73 m^2, did not differ from those of the control group. Compared with the control group, patients had reduced albumin catabolism, 9.76 ± 1.74 g/1.73 m^2/24 hr versus 13.8 ± 0.77 g/1.73 m^2/24 hr ($P < 0.001$). Within the patient group albumin synthesis increased with increased albumin loss. Serum albumin concentration correlated negatively with albumin losses ($P < 0.001$). The CAPD patients maintained albumin homeostasis through decreased albumin catabolism and increased synthesis. All major albumin pools were maintained despite massive albumin loss.

Homéostasie de l'albumine chez des malades en dialyse péritonéale continue ambulatoire. Les vitesses de disparition de l'albumine et des protéines ont été étudiées chez 18 malades en dialyse péritonéale continue ambulatoire (CAPD). Chez neuf malades, des études simultanées de la distribution et du renouvellement de l'albumine ont été effectuées. La perte totale en albumine était de 4,23 ± 1,42 g/1.73 m^2/24 hr; la quantité totale de protéines enlevée était de 8,79 ± 4,21 g/1.73 m^2/24 hr. Bien que ces valeurs soient tout à fait dans l'ordre de grandeur de celles des néphroses sévères, la concentration d'albumine sérique restait pratiquement normale, 3,7 ± 0,5 g/dl. La masse d'albumine plasmatique, 120,0 ± 25,2 g/1,73 m^2, et la masse d'albumine totale, 249 ± 29,1 g/1,73 m^2 n'étaient pas différentes de celles du groupe contrôle. Par rapport au groupe contrôle, les malades avaient un catabolisme de l'albumine réduit, 9,76 ± 1,74 g/1,73 m^2/24 hr contre 13,8 ± 0,77 g/1,73 m^2/24 hr ($P < 0,001$). Dans le groupe de malades, la synthèse d'albumine s'est élvée avec l'augmentation de la perte d'albumine. La concentration d'albumine sérique était négativement corrélée avec les pertes d'albumine ($P < 0,001$). Les malades en CAPD maintenaient une homéostasie de l'albumine grâce à une diminution du catabolisme et à une augmentation de la synthèse d'albumine. Les principaux compartiments de l'albumine étaient maintenus, malgré une fuite massive d'albumine.

Since its introduction in 1979, continuous ambulatory peritoneal dialysis (CAPD) has been widely accepted as a modality for the treatment of endstage renal disease. Loss of protein during this procedure comparable to that that occurs in severe nephrosis has been documented by several investigators [1, 2]. The homeostatic mechanisms triggered in response to albumin loss in patients undergoing CAPD have not been reported. Only modest hypoalbuminemia develops in CAPD patients [2] compared with the severe hypoalbuminemia that is present in nephrotic patients. We were therefore especially interested in studying albumin and protein removal rates and the effect of albumin removal on serum albumin concentration, distribution, and catabolism in patients undergoing CAPD.

Methods

All patients entering or on the CAPD program at the University of California Renal Center at San Francisco General Hospital Medical Center and the San Francisco Veterans Administration Hospital, San Francisco, California, were asked to participate in the study. Informed consent was obtained from all patients and control subjects. Patients who had exit site leaks or severe infections were excluded from the study. One patient dropped out of the study because of the development of a peritoneal pleural fluid communication. The relationship between serum albumin concentration and peritoneal albumin loss was studied in the 18 dialysis patients. Albumin turnover and distribution were studied in nine of these patients. The patients were not receiving prednisone or anabolic steroid therapy. The causes of renal failure are shown in Table 1. Volunteer subjects without proteinuria or known renal abnormalities constituted a control group and were studied as outpatients. Clinical characteristics of this group are shown in Table 2.

Patients were admitted to the General Clinical Research Center at San Francisco General Hospital Medical Center on the day before initiation of the study. A nutritional history was obtained by a dietitian. The patients were then placed on a fixed metabolic diet that was developed from information obtained from the nutritional history. The caloric intake, including dialysate glucose absorption, was designed to be isocaloric, ± 100 calories per day, with the previous dietary record. All subjects received a blocking dose of Lugol's solution on the first day of study. ^{125}I-Albumin (Mallinkrodt, Inc., St. Louis, Missouri), 10 μCi, was injected into a peripheral vein. A total of six blood samples were obtained on day 1 (3 ml/sample) at 5, 15, and 60 min and 2, 5, and 10 hr. An additional sample was drawn

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Table 1. Clinical characteristics of patients undergoing continuous ambulatory peritoneal dialysis

Patient no.	Age/Sex *years*	Renal disease	Serum characteristics: Blood urea nitrogen *mg/dl*	Creatinine *mg/dl*	Hematocrit *%*	Calorie intake *Kcal/kg/day*	Dietary protein intake *g/kg/day*	Treatment for endstage renal disease *months*	Time on peritoneal dialysis *months*
1	66/F	Unknown	81	8.8	22	33	1.1	1	1
2	61/M	Polycystic	82	9.7	46	38	1.4	1	1
3	38/M	Diabetes mellitus	76	20.5	25	38	1.4	18	18
4	42/M	Diabetes mellitus	62	10.2	24	42	1.2	1	1
5	52/M	Diabetes mellitus	73	7.9	29	38	1.35	4	4
6	30/M	Chronic glomerular nephritis	108	9.3	22	42	1.52	60	1
7	74/M	Unknown	67	9.4	34	31	1.03	39	38
8	62/M	Unknown	103	9.9	35.2	20	0.85	6	2
9	39/M	Unknown	81	8.6	25.8	43	1.53	1	1
10	29/F	Diabetes mellitus	48	6.0	21	44	2.0	37	1
11	52/F	Unknown	51	17.0	20	39	1.5	60	1
12	51/M	Chronic glomerular nephritis	60	15.3	19	27	0.8	61	1
13	53/M	Chronic glomerular nephritis	89	11.2	35	50	1.5	108	1
14	29/M	Diabetes mellitus	125	18.3	23	37	1.5	18	3
15	55/M	Chronic glomerular nephritis	76	20.3	27	64	1.5	96	1
16	37/M	Obstructive uropathy	85	19.5	27	26	0.97	48	1
17	67/F	Unknown	93	12.0	31	34	1.5	32	1
18	63/F	Unknown	73	15.1	32	40	1.33	77	1

Table 2. Clinical characteristics and albumin homeostatic data for five control subjects

Patient no.	Age/sex *years*	Weight *kg*	Surface area m^2	Blood urea nitrogen *mg/dl*	Creatinine *mg/dl*	Hematocrit *%*	Serum albumin *g/dl*	Plasma volume, liter *(ml/kg)*	Plasma albumin mass, g *(g/1.73 m^2)*	Total albumin mass, g *(g/1.73 m^2)*	Extravascular albumin mass, g *(g/1.73 m^2)*	$\frac{PAM}{EVAM}$	Albumin synthesis/catabolism, g/24 hr *(g/24 hr/ 1.73 m^2)*	Fractional catabolism *% PAM/ 24 hr*
1	39/M	75.0	1.92	19.6	0.9	41	4.51	2.314 (30.9)	104.0 (93.7)	271 (244)	166 (150)	0.627	14.97 (13.49)	14.4
2	41/M	82.3	2.06	17.3	1.0	43	4.49	3.149 (38.3)	141.0 (118)	314 (264)	172 (144)	0.820	16.35 (13.73)	11.6
3	41/M	59.0	1.72	8.0	0.9	45	4.64	2.170 (36.7)	100.0 (101)	237 (238)	136 (137)	0.735	14.71 (14.79)	14.7
4	39/M	75.0	2.00	17.4	1.0	43	4.80	2.807 (37.4)	135.0 (117)	353 (305)	218 (189)	0.619	16.48 (14.25)	12.2
5	30/F	56.4	1.63	12.7	0.8	38	4.73	2.288 (40.6)	108.0 (115)	264 (280)	156 (165)	0.692	12.02 (12.76)	11.1

Abbreviations: EVAM, extravascular albumin mass; PAM, plasma albumin mass.

24 hr after the injection and daily for 2 weeks and then twice weekly for a total time of 4 weeks from the time of injection. Blood was obtained from control subjects twice weekly after the initial 48-hr period.

Dialysate and urine were collected daily for the measurement of total protein and albumin. Each blood sample was also assayed for total protein and albumin. Total ^{125}I-radioactivity per milliliter and per milligram of albumin was measured in each of these fluids.

Laboratory methods. Total protein in serum, dialysate, and urine were measured by the method of Bradford [3]. Albumin was determined by immunoelectrophoresis [4] in all samples and in addition by the bromcresol green dye indicator in serum samples [5]. To determine the specific radioactivity of ^{125}I bound to albumin, each dialysis sample was passed through an Affi-Gel Blue affinity column obtained from BioRad, Richmond, California. The gel was suspended in an equal volume of 20 mM potassium phosphate, pH 7.1. The slurry was placed in a disposable plastic column (BioRad). A total bed volume was 0.5 ml. Each column was washed with 1.5 ml of the phosphate buffer. Twenty milliliters of dialysate were then slowly applied to the column. The column was washed with several volumes of the phosphate buffer and the eluate was discarded. Albumin was eluted with 1 ml of 8 M urea in phosphate buffer. The eluate was dialyzed extensively against four changes of distilled water and then lyophilized. Purity of albumin was confirmed by

Table 3. Parameters of albumin homeostasis in 18 patients undergoing CAPD

Patient no.	Weight *kg*	Surface area m^2	Serum albumin *g/dl*	Plasma volume, liter *(ml/kg)*	Plasma albumin mass, *g (g/1.73 m^2)*	Total albumin mass, *g (g/1.73 m^2)*	Extra vascular albumin mass, *g (g/1.73 m^2)*	$\frac{PAM}{EVAM}$	Dialysis protein loss, g/24 hr *(g/24 hr/ 1.73 m^2)*	Urinary protein loss, g/24 hr *(g/24 hr/ 1.73 m^2)*	Total protein loss, g/24 hr *(g/24 hr/ 1.73 m^2)*
1	53.4	1.32	3.9	2.29 (42.8)	90.0 (117)	193 (252)	103 (135)	0.874	6.48 (8.49)	0.595 (0.779)	7.08 (9.27)
2	65.5	1.77	4.0	2.99 (45.7)	126 (123)	264 (258)	138 (135)	0.913	9.53 (9.32)	0.611 (0.598)	10.14 (9.92)
3	64.8	1.76	3.7	3.69 (55.6)	133 (131)	315 (310)	182 (180)	0.731	13.1 (12.9)	0.187 (0.184)	13.3 (13.1)
4	80.0	2.06	2.6	8.14 (102)	210 (176)	327 (273)	117 (97.3)	1.745	7.94 (6.66)	12.17 (10.22)	20.1 (16.9)
5	77.7	2.00	3.8	2.65 (34.1)	101 (87.4)	269 (232)	168 (145)	0.601	6.44 (5.57)	1.03 (0.891)	7.47 (6.46)
6	54.5	1.65	3.9	2.90 (53.2)	113 (119)	204 (214)	91 (95.3)	1.242	3.44 (3.60)	0 (0)	3.44 (3.61)
7	69.0	1.86	3.6	2.64 (38.3)	95 (93.4)	246 (228)	151 (140)	0.629	9.30 (8.65)	0.564 (0.525)	9.86 (9.18)
8	85.1	1.88	4.5	2.81 (32.9)	126 (116)	248 (228)	122 (112)	1.03	5.78 (5.32)	0.22 (0.20)	6.00 (5.52)
9	62.8	1.66	3.7	3.19 (50.9)	115 (120)	236 (246)	121 (126)	0.95	3.41 (3.55)	1.56 (1.63)	4.97 (5.18)
10	45.0	1.45	2.4						19.8 (23.6)	0 (0)	19.8 (23.6)
11	62.5	1.69	3.3						13.0 (13.31)	0 (0)	13.0 (13.3)
12	77.2	1.86	3.7						13.9 (13.0)	0 (0)	13.9 (13.0)
13	62.5	1.80	3.3						18.9 (18.2)	0 (0)	18.9 (18.2)
14	85.0	2.10	4.1						14.5 (11.94)	2.01 (1.66)	16.5 (13.6)
15	55.9	1.68	3.9						8.8 (9.06)	0 (0)	8.8 (9.06)
16	95.5	2.20	4.1						11.7 (9.20)	0.546 (0.430)	12.2 (9.63)
17	55.5	1.60	3.5						8.8 (9.52)	0.180 (0.197)	8.98 (9.72)
18	62.3	1.71	4.4						9.7 (9.81)	0 (0)	9.7 (9.81)

discontinuous gel electrophoresis [6]. Each sample was then counted in a spectrometer (Model 3002, Auto Gamma Spectrometer, Packard, Downers Grove, Illinois) with a counting efficiency of 71%.

Calculations of albumin catabolism and distribution. Because inorganic iodide clearance would be anticipated to be prolonged in dialysis patients compared with subjects with normal renal function, inorganic iodide was removed from each serum sample by passage through a column of BioRad AG 1X8 (BioRad) resin (Cl^- form) to remove free ^{125}I. The eluate was assayed for albumin [4, 5] and counted for ^{125}I. This allowed us to determine the specific radioactivity of serum albumin unaffected by retained inorganic iodide. All ^{125}I counts were confirmed to be precipitable by 10% trichloroacetic acid. ^{125}I disintegrations per minute were determined per milliliter of serum normalized to the mean serum albumin concentration for each patient.

Calculations. The logarithm of the counts bound to albumin per milliliter of plasma is plotted versus time. The area under the resulting curve (AUC) is computed in two parts using the log trapezoidal equation. The area from C_o to the last measured concentration C_{last} is integrated using the following equation. The area under each segment is determined for each of the C_n's and the areas are then added together.

$$\frac{(C_n - C_{n-1})(\Delta T)}{\ln C_n - \ln C_{n-1}} \quad (1)$$

The area from C_{last} to infinity is integrated by the equation:

$$\frac{C_{last}}{\beta} \quad (2)$$

where β is the final time constant, ln2/T1/2, estimated by fitting four or more data points in the final log-linear portion of the curve to a monoexponential equation. The terminal portion made up approximately 20% of the total AUC where AUC was the total area [7]:

Table 3. *(Continued)*

Dialysis albumin loss, g/24 hr *(g/24 hr/ 1.73 m²)*	Urinary albumin loss, g/24 hr *(g/24 hr/ 1.73 m²)*	Total external albumin loss, g/24 hr *(g/24 hr/ 1.73 m²)*	Albumin synthesis, g/24 hr *(g/24 hr/1.73 m²)*	Albumin catabolism, g/24 hr *(g/24 hr/ 1.73 m²)*	Fractional elimination rate *(% PAM/24 hr)*	Fractional catabolic rate *(% PAM/24 hr)*
2.09	0.175	2.27	8.71	6.44	9.68	7.16
(2.74)	(0.229)	(2.98)	(11.41)	(8.43)		
3.48	0.206	3.69	17.28	13.59	13.7	10.8
(3.40)	(0.202)	(3.60)	(16.89)	(13.29)		
4.86	0.08	4.94	16.69	11.75	12.5	8.84
(4.78)	(0.08)	(4.86)	(15.91)	(11.05)		
4.60	4.28	8.88	21.67	12.79	10.3	6.09
(3.86)	(3.61)	(7.47)	(18.19)	(10.72)		
3.68	0.694	4.37	15.4	11.03	15.2	10.9
(3.18)	(0.601)	(3.78)	(13.32)	(9.54)		
2.98	0	2.98	11.33	8.35	10.0	7.4
(3.13)	(0)	(3.13)	(11.88)	(8.75)		
5.53	0.054	5.58	15.16	9.58	16.0	10.1
(5.15)	(0.050)	(5.20)	(14.10)	(8.90)		
3.50	0.220	3.72	14.33	10.61	11.40	8.42
(3.22)	(0.20)	(3.42)	(13.19)	(9.77)		
2.84	0.673	3.51	10.60	7.09	9.22	6.17
(2.96)	(0.701)	(3.66)	(11.05)	(7.39)		
11.0	0	11.0				
(13.1)	(0)	(13.12)				
9.0	0	9.0				
(9.21)	(0)	(9.21)				
5.0	0	5.0				
(4.65)	(0)	(4.65)				
9.5	0	9.5				
(9.13)	(0)	(9.13)				
6.80	0.95	7.75				
(5.60)	(0.786)	(6.39)				
3.70	0	3.7				
(3.81)	(0)	(3.81)				
6.8	0.113	6.91				
(5.35)	(0.104)	(5.45)				
3.3	0.016	3.3				
(3.54)	(0.018)	(3.56)				
4.8	0	4.80				
(4.86)	(0)	(4.86)				

$$\text{AUC} \infty = \int_0^\infty C_n dt. \qquad (3)$$

The counts per minute per milliliter of plasma bound to albumin were used in these calculations. The dose (D) (total counts injected) divided by AUC is the clearance of albumin in milliliters per hour [8]. The product of the clearance and the mean serum albumin concentration is then the total removal rate of albumin by all routes. When the linear trapezoidal rule was used as the method of integration, rather than the log trapezoidal rule, the results differed by less than 1%, since the time intervals between sampling were much less than the half-life. The subjects' weight, with the exception of patient no. 4, and serum albumin concentration remained constant throughout the course of these measurements. We therefore made the assumption that these patients were in a steady state so that total albumin turnover was equal to the average rate of albumin synthesis. In the absence of exudative skin lesions or a protein-losing enteropathy, albumin is removed only by catabolism, urinary loss, and peritoneal losses. The metabolic component of albumin loss is due to endogenous catabolism of albumin and is then total loss minus extracorporeal losses and is defined

$$\begin{aligned}\text{Albumin catabolism} = \\ \text{D/AUC} \times (\text{serum albumin concentration}) \\ - (\text{urinary loss} + \text{peritoneal loss})\end{aligned} \qquad (4)$$

Steady state volume of distribution was measured by the method of Benet and Galeazzi [9]. In this method the area under the first moment curve (AUMC) of the plasma ^{125}I concentration is defined as the area under the curve of the product of time, t, and plasma concentration, C_n, from zero time to infinity [7].

$$\text{AUMC} \infty = \int_0^\infty tC_n dt \qquad (5)$$

The steady state volume of distribution is then [7]

$$VD_{ss} = \frac{\text{dose} \times [\int_0^\infty {}^tC_n dt]}{[\int_0^\infty C_n dt]^2} = \frac{\text{dose } [\text{AUMC}_o \rightarrow \infty]}{[\text{AUC}_o \rightarrow \infty]^2} \qquad (6)$$

This determination is valid when elimination occurs exclusively from the central (plasma) compartment of a multicompartment model [9], but that is true of all other methods used for determining the apparent volume of distribution of a substance. The assumption is also valid with respect to albumin metabolism [10].

The integral of $\text{AUMC}_o \rightarrow \infty$ is again done in two parts. We have chosen to use the log trapezoidal equations again rather than the linear trapezoidal equations, although the difference in results between the two methods is again quite small in this case.

The area from C_o to C_{last} is calculated by summing the areas for n = 1 to n = last measured [7]:

$$\frac{t_n C_n - t_{n-1} C_{n-1}}{(1/\Delta t) \ln (C_n/C_{n-1})} - \frac{C_n - C_{n-1}}{[(1/\Delta t) \ln (C_n/C_{n-1})]^2}. \qquad (7)$$

The area from C_{last} at t_{last} to ∞ is given by [7]:

$$\frac{t_{last} C_{last}}{\beta} + \frac{C_{last}}{\beta^2}. \qquad (8)$$

Plasma volume is determined after bolus injection of ^{125}I human serum albumin intravenously. Blood samples obtained at 5, 15, and 60 min are assayed for counts per minute per milliliter. The results are extrapolated to zero time using least squares regression to a semilogarithmic plot. Plasma albumin mass is plasma volume times serum albumin concentration.

Fractional albumin catabolism is defined as the portion of the plasma albumin pool catabolized per 24 hr [11–13]; similarly, fractional albumin elimination rate is defined as the portion of the plasma albumin pool eliminated per 24 hr. Both are expressed as percent. Total albumin elimination is equal to albumin catabolism plus total external albumin loss. Total albumin mass is then defined as plasma albumin concentration times VD_{ss}. Extravascular albumin mass is total albumin mass − plasma albumin mass. Student's *t* test was used for analysis of unpaired data.

Table 4. Comparison of albumin homeostasis in patients undergoing CAPD with normal control patients and with nephrotic patients

Parameter	Normal control group $N = 5$	CAPD patients $N = 9$	Significance normal compared to CAPD	Nephrotic patients $N = 30$	Significance nephrotic patients compared to CAPD patients
Age, *years*	38.00 ± 4.6	50.0 ± 14.1	NS		
Weight, *kg*	69.5 ± 11.3	68.1 ± 11.0	NS	67.5 ± 11.25	NS
Serum albumin, *g/dl*	4.6 ± 0.3	3.7 ± 0.5	<0.005	1.54 ± 0.68	<0.001
Plasma volume, *ml/kg*	36.8 ± 3.6	50.6 ± 20.9	NS	48.5 ± 10.5	NS
Plasma albumin mass, *g/1.73 m²*	108.9 ± 10.9	120.0 ± 25.2	NS	48.1 ± 22.2	<0.001
Total body albumin mass, *g/1.73 m²*	266.2 ± 27.3	249.0 ± 29.1	NS	92.1 ± 44.6	<0.001
Extravascular albumin mass, *g/1.73 m²*	157.0 ± 20.7	130.0 ± 26.2	NS	43.3 ± 22.1	<0.001
Plasma albumin mass / Extravascular albumin mass	0.699 ± 0.083	0.968 ± 0.354	NS	1.187 ± 0.402	NS
External albumin loss, *g/1.73 m²*	0	4.23 ± 1.42	<0.001	6.6 ± 2.67	<0.05
Protein loss, *g/1.73 m²*	0	8.79 ± 4.21	<0.001	8.87 ± 3.88	NS
Catabolism, *g/24 hr/1.73 m²*	13.80 ± 0.77	9.76 ± 1.74	<0.001	6.48 ± 1.97	<0.001
Synthesis, *g/24 hr/1.73 m²*	13.80 ± 0.77	13.99 ± 2.52	NS	13.56 ± 2.8	NS

Results

Table 3 summarizes albumin homeostatic data for the 18 patients. Serum albumin concentration remained constant in all patients except patient no. 4. In that patient, serum albumin concentration rose from 2.6 to 3.2 g/dl in association with a 6.9-kg weight loss. That loss was the result of negative fluid balance achieved to obtain control of the patient's hypertension. Daily peritoneal and urinary albumin losses did not vary significantly during the study period in that patient. Albumin losses for the group ranged from 2.98 g to 13.12 g/1.73 m^2. Protein losses ranged from 3.61 g to 23.6 g/1.73 m^2/24 hr. Despite those losses, the plasma albumin pool and the ratio of plasma albumin to extravascular albumin remained within the normal range in our CAPD patients. The serum albumin concentration for the 18 CAPD patients was 3.7 ± 0.5 g/dl with an extracorporeal albumin loss of 5.46 ± 2.70 g/1.73 m^2/24 hr. Albumin synthesis was increased above the normal range in two of our patients. Table 4 compares the albumin homeostatic data in nine CAPD subjects in whom albumin distribution and synthesis were studied with those of five normal control subjects. Albumin catabolism was significantly less in the patients than in the control subjects.

Figure 1 shows a negative correlation between serum albumin concentration and peritoneal albumin losses in 18 CAPD patients.

Multiple linear regression analysis was performed in the nine patients in whom albumin turnover studies were carried out to determine whether or not plasma volume expansion made a significant contribution to hypoalbuminemia, as we have shown to be true in rats with chronic renal failure [14]. The relationship between serum albumin concentration and both plasma volume and external albumin loss was analyzed using multiple regression analysis [15].

$$\text{Albumin concentration} = 5.069 - (0.173 \pm 0.091) \times \text{albumin loss (g/1.73 m}^2\text{/24 hr)} - (0.0117 \pm 0.0062) \times \text{plasma volume (ml/kg)} \quad (9)$$

The SD of the regression was 0.221 ($r = 0.9246$, $P < 0.001$). The partial correlation coefficients were for albumin loss ($r = 0.8765$, $P < 0.002$, and for plasma volume $r = 0.8758$, $P = 0.002$).

Figure 2 shows the change in specific radioactivity of ^{125}I-labeled albumin in the serum of one of our peritoneally dialyzed patients. It also shows the relationship between the specific radioactivity of albumin removed by peritoneal dialysis and the plasma concentration of specific radioactivity of plasma albumin. Although Figure 2 was derived from only one patient, the results were the same for all patients studied. It takes between 1 and 2 days before the peritoneal albumin specific radioactivity equals the plasma albumin concentration. After that time, the specific radioactivity of peritoneal albumin overshoots the plasma level and remains slightly above the plasma value thereafter.

Figure 3 shows the relationships among albumin synthesis, albumin catabolism, and total extracorporeal loss of albumin. Although catabolism remained constant, albumin synthesis increased with increasing extracorporeal losses within the nine patients.

Discussion

Our CAPD patients suffered large external losses of albumin and other proteins well within the nephrotic range [11, 16–19]. Although the fall in serum albumin concentration was highly significant in comparison to our control subjects, it was quite small (0.9 g/dl). It is instructive to compare the state of albumin metabolism in our CAPD patients with that of albumin metabolism of some nephrotic patients studied by other investigators [11, 16–19]. A characteristic of nephrotic syndrome is the complete lack of correlation between serum albumin concentration and albuminuria or proteinuria [11, 16]. In CAPD patients, there is a striking correlation between albumin losses and serum albumin concentration, but the serum albumin concentration falls only modestly with increasing extracorporeal losses. Part of the fall in serum albumin concentration is the result of plasma

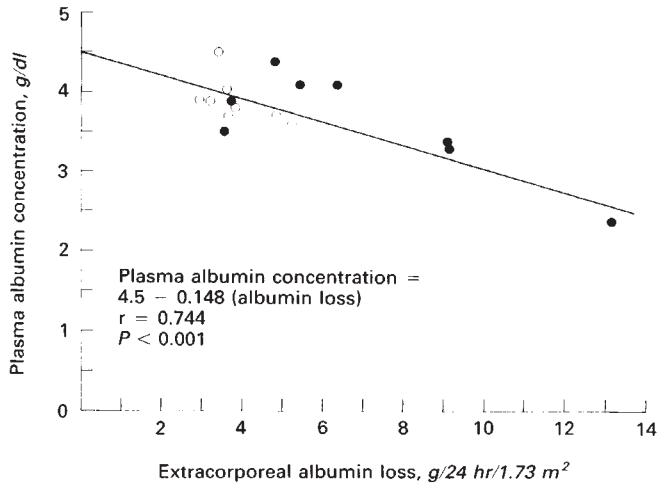

Fig. 1. *Relationship between serum albumin concentration and total extracorporeal albumin loss per day per 1.73 m² (peritoneal + urinary).* Symbols are: ●, data points for patients in whom no albumin turnover studies were performed; ○, data points from patients in whom albumin turnover studies were performed.

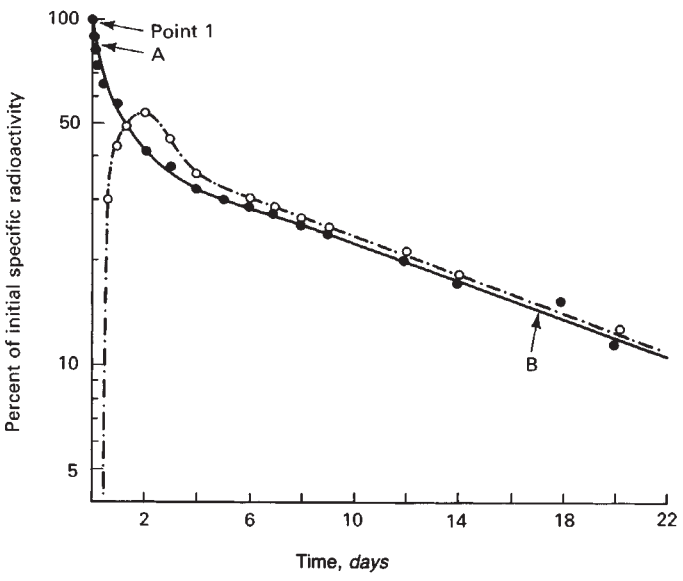

Fig. 2. *Specific radioactivity of serum (●, ——) and peritoneal albumin (○, ------) in patient no. 2 with chronic ambulatory peritoneal dialysis.* The rapid component (**A**) of this curve was extrapolated to zero time (Point 1). Plasma volume is the ratio of injected dose in counts per minute (CPM) to the extrapolation at the zero time of the ^{125}I plasma curve expressed in CPM/ml. The terminal component (**B**) was used to calculate the volume of distribution of albumin as described in **Results**.

volume expansion. We have demonstrated previously that serum albumin concentration in rats with chronic renal failure is depressed independently by both external loss and by plasma volume expansion [14]. This is also the case in patients on CAPD. Plasma albumin mass, total albumin mass, and distribution of albumin were not different when the CAPD patients and normal control subjects were compared.

Jensen et al [11] studied 30 nephrotic patients and reported a mean urinary albumin loss of 6.60 ± 2.67 g/1.73 m²/24 hr with a serum albumin concentration of 1.54 ± 0.68 g/dl. Six patients studied by Kaitz [17] had a mean albumin loss of 6.9 ± 3.4 g/24 hr with a serum concentration of 2.28 ± 1.14 g/dl. Six patients studied by Bauman et al [18] had a mean urinary albumin loss of 6.43 ± 3.39 g/70 kg/24 hr with a serum albumin concentration of 2.90 ± 0.94 g/dl. Five patients studied by Blahd, Fields, and Goldman [19] had a mean urinary albumin loss of 7.53 ± 2.24 g/24 hr with a serum albumin concentration of 1.00 ± 0.37 g/dl; no weights were given for their patients. External albumin losses for our 18 CAPD patients were 5.61 ± 2.59 g/1.73 m²/24 hr. In no case was the difference between albumin lost by our 18 CAPD patients and that lost by the nephrotic patients in any of the studies just cited statistically significant. In all cases the serum albumin concentration was significantly higher in the CAPD patients than in the nephrotic patients. The studies by Jensen et al [11] and Gitlin, Janeway, and Farr [16] provide both height and weight for their patients. The study by Jensen et al [11] is the largest study reported, and so their data can be more readily compared with our own. Albumin excretion calculated from their data and serum albumin concentration reported for nephrotic patients are very similar to those reported by the other groups and thus appear to be representative of the nephrotic patient population. In contrast to CAPD patients, nephrotic patients have a markedly reduced plasma albumin pool. The extravascular pool is depleted to an even greater extent [11, 16]. There are three potential mechanisms for adapting to external albumin loss; these are as follows:

(1) Albumin synthetic rate may be increased. Within our CAPD patient population, albumin synthesis was increased gram for gram with increasing external albumin loss. In one study albumin synthesis in nephrotic children was increased twofold over the control group [20], but the control group consisted of patients who would be expected to have reduced albumin synthesis [21] (one with anorexia nervosa, one with cystic fibrosis, one with chronic liver disease, and one mentally retarded child with undefined nutritional status). Within the group of patients described by Jensen et al [11], albumin synthesis tended to increase with increasing urinary albumin losses. Bianchi et al [22] suggested that albumin synthesis increases linearly with urinary albumin excretion in patients with albuminuria approaching 33 g/day. They unfortunately did not measure either urinary albumin or protein excretion directly, but calculated it from the ratio of bound to unbound ^{125}I in the urine. If their patients did indeed excrete 33 g of albumin in their urine per day, increased albumin synthesis must have played an important role because reduction in albumin catabolism to zero could only provide about 14 g of albumin for external loss. They argued that the stimulus for increased albumin synthesis in nephrotic patients is the depeletion of the extravascular albumin pool. They are not alone in their hypothesis that depletion of the extravascular albumin pool or of a particular extravascular pool is of key importance in the regulation of the rate of albumin synthesis. Rothschild et al [23] and Oratz [24] identified an interstitial pool of albumin in the liver that seemed to act as an oncostat. They demonstrated an inverse relationship between the content of albumin in this interstitial pool and the rate of albumin synthesis. If the depletion of albumin from the interstitium is important in producing increased albumin synthesis in some nephrotic pa-

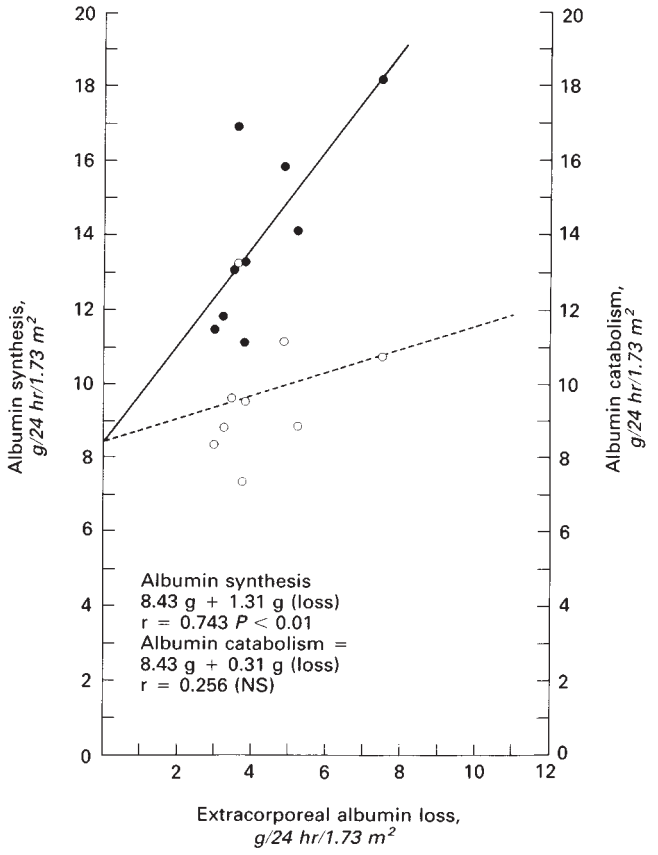

Fig. 3. *Response of albumin synthesis* (●, ——) *and albumin catabolism* (○, ------) *of chronic ambulatory peritoneal dialysis patients to increasing extracorporeal albumin loss.*

tients, depletion of the entire interstitial albumin pool in CAPD patients cannot be the mechanism responsible for increased albumin synthesis within that group of patients. The interstitial albumin pool is normal in the CAPD patients, unlike in nephrotic patients where it is depleted [11, 16].

(2) Albumin catabolism may be reduced and was reduced in our patients as a group in comparison with control subjects. Albumin catabolic rate did not vary within the CAPD patient population when patients with larger albumin losses were compared with those with lesser losses. It is, therefore, not possible to tell whether or not the reduced albumin catabolic rate was a response to external albumin loss. In examining the data of Jensen et al [11] and Gitlin, Janeway, and Farr [16], albumin catabolism was reduced in nephrotic patients also. The difference between normal synthesis rates and depressed catabolic rates provides the excess albumin that is lost through the kidney in their patients. Historically, increased renal catabolism of albumin is considered a major contributing factor in the generation of hypoalbuminemia, but albumin catabolism is, in fact, not increased in absolute terms. Absolute albumin catabolic rate was greater in our CAPD patients than in Jensen's nephrotic patients, and total albumin loss, through catabolism and direct external losses, tended to be greater in our patients than in their nephrotic patients. Since albumin catabolism was in steady state in these patients, albumin synthesis also tended to be greater in the CAPD patients.

(3) Albumin may be transferred from the extravascular compartment to the vascular compartment. This has been shown to be important in the acute adaption of rats to albuminuria [25]. This process mobilizes a limited reserve of albumin but clearly must play a role in nephrotic humans as evidenced by the depleted extravascular albumin pool. This mechanism is not important in CAPD patients because the extravascular pool is normal.

Another principal difference between the CAPD patients and nephrotic patients is the route of albumin loss. Nephrotic patients filter serum proteins directly from the circulation so the plasma compartment is depleted directly [26–29]. During peritoneal dialysis, the plasma compartment is depleted of albumin only indirectly. Bonomini, Zucchelli, and Mioli [30] demonstrated that during the initiation of peritoneal dialysis there was a pool of nonradioactive albumin that was mobilized after injection of ^{125}I-labeled albumin into a peripheral vein. They estimated this pool to be about 6 g, and presumably, it represents an interstitial pool of albumin. Our data are consistent with this interpretation. The lag in the specific radioactivity of albumin in dialysate behind that in plasma was due to a lag in transport of albumin from the vascular compartment into the interstitial compartment that was then depleted by the dialysis procedure. The reason the specific radioactivity of albumin in the dialysate was higher than that in plasma after day 2 was because the interstitial pool in the abdomen represented albumin from the vascular compartment from an earlier time point when the specific radioactivity of serum albumin was higher than that in a blood sample obtained simultaneously when the dialysate sample was collected. The albumin in the dialysate came from the extravascular interstitial pool. Depletion of an extravascular pool of albumin rather than a vascular pool might be significant. If the rate of albumin synthesis is indeed regulated by an oncotically sensitive pool in the abdomen as proposed by Rothschild et al [23] and Oritz [24], peritoneal dialysis might act by depleting that pool directly and therefore directly stimulate albumin synthesis. In nephrotic patients this pool would be depleted indirectly because the pool would be in equilibrium with, but not directly contiguous with, the serum compartment. Patients with the nephrotic syndrome would then be able to increase the rate of albumin synthesis but at the expense of a depleted plasma pool.

Clearly, there are other differences between the nephrotic patients described by other investigators [11, 16–19] and our CAPD patients. The CAPD patients have continuous peritoneal absorption of glucose and the many endocrinologic and metabolic perturbations of endstage renal disease. It may be argued that patients with the nephrotic syndrome may have proteinuria for long periods of time prior to study, but, to our knowledge, there have been no studies to indicate that there is a qualitative change in albumin metabolism in nephrotic patients as the duration of albuminuria is prolonged. We found no difference in albumin metabolism in CAPD patients who had been dialyzed for up to 38 months. Other studies on CAPD patients have failed to show deterioration of serum albumin concentration with longer times on dialysis [31]. Many of our patients were studied shortly after the onset of peritoneal dialysis. It might be argued that a contributing mechanism of albumin homeostasis in these patients was mobilization of the extravascular albumin mass. Serum albumin concentration remained stable through

the 4 weeks of study, as did peritoneal albumin losses. Serum albumin concentration also remained stable for several months after these studies were performed. These observations would indicate that metabolic processes—decreases in catabolism or increases in synthetic rate—replaced the albumin lost rather than mobilization of a finite extravascular pool. When dialysis patients with protein intakes of 1.53 g/kg body wt were compared with those who consumed less generous quantities of protein, down to 0.85 g/kg body wt, or when diabetic patients and patients with other forms of renal failure were compared, their responses to albumin losses were indistinguishable. The CAPD patients through combined mechanisms of increasing albumin synthesis within the group in direct response to external albumin loss and of reducing albumin catabolism in comparison with control subjects accomodate for albumin losses with little or no derangements in albumin concentration, pool size, or distribution.

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